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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,144	09/26/2003	Lawrence Tamarkin	CYT-0027	8073

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Johnson & Associates
317A E. Liberty Street
Savannah, GA 31401

EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
02/15/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,144	TAMARKIN ET AL.	
	Examiner	Art Unit	
	J. E. ANGELL	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,31 and 40-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,31 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 12/6/2010.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Applicant's election without traverse of the species polyclonal antibodies in the reply filed on 12/6/2010 is acknowledged.

It is noted, however, that a search for the claims with the elected species did not identify any prior art that taught or suggested the elected species of targeting molecules, therefore the search was expanded to the other claimed species.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 10/14/2010 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 31, 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 31 recites the phrase "vascular epithelial growth factor ("VEGF")." However "vascular epithelial growth factor ("VEGF")" is unclear because there is no particular definition of the term in the specification and it does not appear to be recognized in the prior art. It is noted that the term "vascular endothelial growth factor" is recognized in the art as "VEGF", but the art also recognizes the term "Epithelial Growth Factor" as well as "Endothelial Growth Factor" known as "EGF". Therefore, without a clear indication of the term "vascular epithelial growth factor ("VEGF")" and considering that the art recognizes more than one alternative very similar to the term, the term "vascular epithelial growth factor ("VEGF") is unclear. Claim 40-42 are included in the rejection because they are dependent claims.

5. It is noted that should Applicant make an amendment, they should provide the page and line numbers where support for the amendment can be found.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fitzgerald et al. (Cell 1983, cited in 10/14/2010 IDS) in view of Leizer et al. (Blood 76(10), 1990; pages 1989-1996).

9. Fitzgerald et al. teach a method of delivering Epidermal Growth Factor (EGF) into a cell using colloidal gold wherein EGF and adenovirus are attached to the colloidal gold (e.g., see abstract). It is noted that although Fitzgerald et al. do not specifically teach that EGF is a cytokine, EGF is recognized as a cytokine as evidenced by Leizer et al., who specifically recognize a number of different cytokines including IL-3, Interferon gamma, IL-2, and EGF (see abstract). Fitzgerald et al. indicates that EGF can be conjugated with Pseudomonas Exotoxin (PE) which is a toxin that acts in the cytosol, is toxic to cancer cells, and is five times more toxic when conjugated with EGF compared to unconjugted PE (e.g., see page 607 second column, page 611, second column). Importantly, Fitzgerald et al. also teach that using the colloidal gold complex comprising adenovirus and PE-EGF attached to the gold, enhanced the PE-EGF toxicity in KB tumor cells (e.g., see page 613).

10. Fitzgerald et al. also teach that adenovirus enters its target cell via internalization by a receptor-mediated process (e.g., see page 607 second column). It is noted that although the specification does not particularly define the term "target molecule" it is clear that the term

encompasses molecules that bind to a receptor on the cell surface (e.g., see paragraphs [0085], [0088], etc.).

11. As such, Fitzgerald teaches a method of using a colloidal gold complex to deliver a cytokine into a cell wherein a cytokine (EGF) and a target molecule (adenovirus) are attached to the colloidal gold.

12. Fitzgerald does not teach administration of the colloidal gold complex is administered to a human or animal.

13. However, Fitzgerald et al. teach that their results demonstrate that "adenovirus disrupts receptosomes, enhancing delivery of material contained in them into the cytosol" (see abstract); and, "We have shown that the interaction of adenovirus with cells allows for the introduction of a cointernalized ligand directly in the cytosol. In this sense, adenovirus entry is analogous to existing procedures for mechanical microinjection…Whatever the mechanism, a potentially valuable biological approach is available for the introduction of materials directly into the cytosol." (See page 615, bottom of first column). Thus, Fitzgerald et al. indicate that the method is valuable (i.e., "useful") for delivering material into cells, including delivering cytotoxic agents, such as PE-EGF, into tumor cells.

14. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to use the method taught by Fitzgerald et al. in a human or animal with a reasonable expectation of success. The motivation to perform the method in a human or animal would be to treat a tumor in a human or animal using the gold complex taught by Fitzgerald et al., especially considering that using the adenovirus/PE-EFG/gold complex was more toxic than PE-EGF alone.

15. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fitzgerald et al. (Cell 1983, cited in 10/14/2010 IDS) in view of Lorberboum-Galski et al. (PNAS 85, 1988; pages 1922-1926).

16. The teachings of Fitzgerald et al. as they apply to the instant claims are described above.

17. Fitzgerald et al. do not teach that the cytokine is IL-2.

18. However, Lorberboum-Galski et al. teach that the cytokine IL-2 can be fused with Pseudomonas Exotoxin (PE), creating a IL-2-PE fusion protein which is "extremely toxic" in a T–cell lymphoma tumor cell types known as HUT-102 (e.g., see abstract; page 1924, second column; etc.). Lorberboum-Galski et al. also teach that the IL-2-PE fusion protein could be useful for treatment of a number of different diseases (e.g., see page 1926, bottom of first column).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the IL-2-PE fusion protein of Lorberboum-Galski et al. for the PE-EGF fusion protein in the gold complex used in the method of Fitzgerald et al. and to use the substituted gold complex to treat disease in an animal or human with a reasonable expectation of success, thus creating the claimed invention.

It is noted that the IL-2-PE and PE-EGF are considered equivalent agents as both are fusion proteins comprising Pseudomonas exotoxin (PE) conjugated with a cytokine that are cytotoxic to tumor cells.

Furthermore, regarding the substitution of equivalents known for the same purpose, MPEP 2144.06 states,

> "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Nevertheless, one of ordinary skill in the art would have been motivated to use the adenovirus/gold complex of Fitzgerald et al. to deliver the IL-2-PE fusion protein of Lorberboum-Galski et al. to a tumor cell because (a) Lorberboum-Galski et al. teaches that IL-2-PE fusion protein can be toxic to tumor cells, and(b) Fitzgerald et al. specifically teaches that the adenoviral/gold complex can increase the toxicity of a cytokine-PE fusion protein 5 fold compared to administering the cytokine-PE fusion protein alone.

Response to Arguments

19. The Terminal Disclaimer filed 10/14/2010 has been accepted, thus obviating the Double Patenting rejection. Therefore, Applicant's arguments, with respect to the Double Patenting rejection(s) of claim(s) are persuasive, in view of the Terminal Disclaimer. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of for the reasons set forth herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635